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(54) Titre: ETABLISSEMENT DU GENOTYPE DE GENES HUMAINS DE L'UDP-GLUCORONOSYL-TRANSFERASE 2B4 (UGT2B4), 2B7 (UGT2B7) ET 2B15 (UGT2B15)

(57) Abstract

Genetic polymorphisms are identified in the human UGT2B4, UGT2B7 and UGT2B15 genes that alter UGT2B activity. Nucleic acids comprising the polymorphic sequences are used to screen patients for altered metabolism for UGT2B substrates, potential drug-drug interactions, and adverse/side effects, as well as diseases that result from environmental or occupational exposure to toxins. The nucleic acids are used to establish animal, cell and in vitro models for drug metabolism.

(57) Abrégé

Des polymorphismes génétiques ont été identifiés dans les gènes humains de UGT2B4, UGT2B7 et UGT2B15, qui modifient l'activité de UGT2B. Selon l'invention on utilise des acides nucléiques comprenant les séquences polymorphiques pour cribler des patients, à la recherche du métabolisme modifié de substrats UGT2B, d'interactions potentielles médicamenteuses et d'effets secondaires, de même qu'à la recherche de maladies induites par une exposition ambiante ou professionnelle aux toxines. On utilise les acides nucléiques pour établir des modèles animaux, cellulaires et in vitro, du métabolisme des médicaments.

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(57) Abstract

Genetic polymorphisms are identified in the human UGT2B4, UGT2B7 and UGT2B15 genes that alter UGT2B activity. Nucleic acids comprising the polymorphic sequences are used to screen patients for altered metabolism for UGT2B substrates, potential drug-drug interactions, and adverse/side effects, as well as diseases that result from environmental or occupational exposure to toxins. The nucleic acids are used to establish animal, cell and *in vitro* models for drug metabolism.

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Description

GENOTYPING HUMAN UDP-GLUCURONOSYLTRANSFERASE 2B4 (UGT2B4), 2B7 (UGT2B7) and 2B15 (UGT2B15) GENES

INTRODUCTION

The metabolic processes commonly involved in the biotransformation of xenobiotics have been classified into functionalization reactions (phase I reactions), in which lipophilic compounds are modified via monooxygenation, dealkylation, reduction, aromatization, or hydrolysis. These modified molecules can then be substrates for the phase II reactions, often called conjugation reactions, as they conjugate a functional group with a polar, endogenous compound. Drug glucuronidation, a major phase II conjugation reaction in the mammalian detoxification system, is catalyzed by the UDP-glucuronosyltransferases (UGTs) (Batt AM, et al. (1994) Clin Chim Acta 226:171-190; Burchell et al. (1995) Life Sci. 57:1819-31).

The UGTs are a family of enzymes that catalyze the glucuronic acid conjugation of a wide range of endogenous and exogenous substrates including phenols, alcohols, amines and fatty acids. The reactions catalyzed by UGTs permit the conversion of a large range of toxic endogenous/xenobiotic compounds to more water-soluble forms for subsequent excretion (Parkinson A (1996) Toxicol Pathol 24:48-57).

The UGT isoenzymes are located primarily in hepatic endoplasmic reticulum and nuclear envelope (Parkinson A (1996) Toxicol Pathol 24:48-57), though they are also expressed in other tissues such as kidney and skin. UGTs are encoded by a large multigene superfamily that has evolved to produce catalysts with differing but overlapping substrate specificities. Three families, UGT1, UGT2, and UGT8, have been identified within the superfamily. UGTs are assigned to one the subfamilies based on amino acid sequence identity, *e.g.*, UGT1 family members have greater than 45% amino acid sequence identity (Mackenzie *et al.* (1997) Pharmacogenetics 7:255-69).

A single gene encodes several human UGT1 isoforms, the substrate specificity of each of which is thought to arise from differential splicing of a number of substrate-specific 5-prime regions of a single mRNA transcript to a shared 3-prime portion. On the other hand, members of the mammalian UGT2 gene subfamily, which encode the odorant and steroid-metabolizing isoforms, show nucleotide differences in sequence throughout the length of the cDNAs. This suggested that the UGT2 isoenzymes are encoded by several independent genes. The UGT2 genes have been further divided on the basis of their tissue-specific expression patterns into the UGT2A gene subfamily, which encodes

olfactory-specific isoforms, and the UGT2B gene subfamily, which encodes steroid-metabolizing isoforms in the liver. Monaghan *et al.* (1994) Genomics 23:496-499 mapped the UGT2B9 and the UGT2B15 genes to chromosome 4q13, giving a provisional ordering of the genes as UGT2B9-UGT2B4-UGT2B15. The UGT2B subfamily contains phenobarbital-inducible genes, as well as numerous genes that are constitutively expressed and are involved in the glucuronidation of endogenous steroids and biogenic amines (Mackenzie, *et al. supra.*) Evidence suggests that UGT2B4 is exclusively expressed in human liver, and not in human kidney. Levesque *et al.* (1997) Pharmacogenetics 7:317; and Coffman *et al.* (1997) Drug Metabol. and Dispos. 25:1-4, describe UGT2B gene polymorphisms.

Alteration of the expression or function of UGTs may affect drug metabolism. For example, there may be common polymorphisms in the human UGT2B gene that alter expression or function of the protein product and cause drug exposure-related phenotypes. Thus, there is a need in the field to identify UGT2B polymorphisms in order to provide a better understanding of drug metabolism and the diagnosis of drug exposure-related phenotypes.

SUMMARY OF THE INVENTION

Genetic sequence polymorphisms are identified in the UGT2B4, UGT2B7 and UGT2B15 genes, herein generically referred to as "UGT2B genes". Nucleic acids comprising the polymorphic sequences are used in screening assays, and for genotyping individuals. The genotyping information is used to predict an individuals' rate of metabolism for UGT2B substrates, potential drug-drug interactions, and adverse/side effects. Specific polynucleotides include the polymorphic UGT2B4 sequences set forth in SEQ ID NOs:25-38; the polymorphic UGT2B7 sequences set forth in SEQ ID NOs:84-111; and the polymorphic UGT2B15 sequences set forth in SEQ ID NOs:147-164.

The nucleic acid sequences of the invention may be provided as probes for detection of UGT2B locus polymorphisms, where the probe comprises a polymorphic sequence of SEQ ID NOs:25-38; 84-111 and 147-164. The sequences may further be utilized as an array of oligonucleotides comprising two or more probes for detection of UGT2B locus polymorphisms.

Another aspect of the invention provides a method for detecting in an individual a polymorphism in UGT2B metabolism of a substrate, where the method comprises analyzing the genome of the individual for the presence of at least one UGT2B polymorphism; wherein

the presence of the predisposing polymorphism is indicative of an alteration in UGT2B expression or activity. The analyzing step of the method may be accomplished by detection of specific binding between the individual's genomic DNA with an array of oligonucleotides comprising UGT2B locus polymorphic sequences. In other embodiments, the alteration in UGT2B expression or activity is tissue specific, or is in response to a UGT2B modifier that induces or inhibits UGT2B expression.

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

UGT2B Reference Sequences. SEQ ID NOs: 1-6 list the sequence of the reference UGT2B4 exons, where exon 1 is SEQ ID NO:1, exon 2 is SEQ ID NO:2 and so forth. Partial sequence of the flanking introns is included; the boundaries are annotated in the SEQLIST. The cDNA sequence is set forth in SEQ ID NO:7, and the encoded amino acid sequence in SEQ ID NO:8.

SEQ ID NO:39 lists the sequence of the UGT2B7 cDNA sequence, the encoded polypeptide is provided in SEQ ID NO:40. SEQ ID NOs: 41-45 list the sequence of the reference UGT2B7 exons, where exon 1 is SEQ ID NO:41, exon 2 is SEQ ID NO:42 and so forth. Partial sequence of the flanking introns is included; the boundaries are annotated in the SEQLIST.

SEQ ID NO:112 lists the sequence of the UGT2B15 cDNA sequence, the encoded polypeptide is provided in SEQ ID NO:113. SEQ ID NOs:114-118 list the sequence of the reference UGT2B15 exons, where exon 1 is SEQ ID NO:114, exon 2 is SEQ ID NO:115 and so forth. Partial sequence of the flanking introns is included; the boundaries are annotated in the SEQLIST.

Primers. The PCR primers for amplification of polymorphic sequences are set forth as SEQ ID NOs:9-14; 46-66; and 135-146. The primers used in sequencing isolated polymorphic sequences are presented as SEQ ID NOs:15-24; 67-83; and 119-134.

Polymorphisms. Polymorphic sequences of UGT2B4 are presented as SEQ ID NOs:25-38. Polymorphic sequences of UGT2B7 are presented as SEQ ID NOs:84-111. Polymorphic sequences of UGT2B15 are presented as SEQ ID NO:147-164.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Pharmacogenetics is the association between an individual's genotype and that individual's ability to metabolize or react to a therapeutic agent. Differences in metabolism or target sensitivity can lead to severe toxicity or therapeutic failure by altering the relation between bioactive dose and blood concentration of the drug. Relationships between polymorphisms in metabolic enzymes or drug targets and both response and toxicity can be used to optimize therapeutic dose administration.

Genetic polymorphisms are identified in the UGT2B4, UGT2B7 and UGT2B15 genes. Nucleic acids comprising the polymorphic sequences are used to screen patients for altered metabolism for UGT2B substrates, potential drug-drug interactions, and adverse/side effects, as well as diseases that result from environmental or occupational exposure to toxins. The nucleic acids are used to establish animal, cell culture and *in vitro* cell-free models for drug metabolism.

Definitions

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, constructs, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a construct" includes a plurality of such constructs and reference to "the UGT2B nucleic acid" includes reference to one or more nucleic acids and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

UGT2B4 reference sequence. The sequence of human UGT2B4 cDNA may be accessed through Genbank, accession number Y00317, and is provided in SEQ ID NOs:1-7. The amino acid sequence of UGT2B4 is listed as SEQ ID NO:8. The sequence of human UGT2B7 may be accessed through Genbank, accession number 600068, and in the SEQLIST as described above. The sequence of human UGT2B15 may be accessed through Genbak, accession number 600069, and in the SEQLIST as described above. The

nucleotide sequences provided herein differ from the published sequence at certain positions throughout the sequence. Where there is a discrepancy the provided sequence is used as a reference.

The term "wild-type" may be used to refer to the reference coding sequences of UGT2B4, UGT2B7 and UGT2B15, and the term "variant", or "UGT2B" to refer to the provided variations in the UGT2B sequences. The UGT2B4, UGT2B7 and UGT2B15 sequences are generically referred to as "UGT2B", and may be further distinguished by the species, *e.g.* human, mouse, *etc.*, or by the specific gene number, *e.g.* UGT2B4, UGT2B7, *etc.* Where there is no published form, such as in the intron sequences, the term wild-type may be used to refer to the most commonly found allele. It will be understood by one of skill in the art that the designation as "wild-type" is merely a convenient label for a common allele, and should not be construed as conferring any particular property on that form of the sequence.

UGT2B polymorphic sequences. It has been found that specific sites in the UGT2B4, UGT2B7 and UGT2B15 genes sequence are polymorphic, *i.e.* within a population, more than one nucleotide (G, A, T, C) is found at a specific position. Polymorphisms may provide functional differences in the genetic sequence, through changes in the encoded polypeptide, changes in mRNA stability, binding of transcriptional and translation factors to the DNA or RNA, and the like. The polymorphisms are also used as single nucleotide polymorphisms (SNPs) to detect genetic linkage to phenotypic variation in activity and expression of the particular UGT2B protein.

SNPs are generally biallelic systems, that is, there are two alleles that an individual may have for any particular marker. SNPs, found approximately every kilobase, offer the potential for generating very high density genetic maps, which will be extremely useful for developing haplotyping systems for genes or regions of interest, and because of the nature of SNPs, they may in fact be the polymorphisms associated with the disease phenotypes under study. The low mutation rate of SNPs also makes them excellent markers for studying complex genetic traits.

SNPs are provided in the UGT2B4, UGT2B7 and UGT2B15 intron and exon sequences. Tables 4, 7 and 10, and the corresponding sequence listing, provide both forms of each polymorphic sequence. For example, SEQ ID NO:37 and 38 are the alternative forms of a single polymorphic site. The provided sequences also encompass the complementary sequence corresponding to any of the provided polymorphisms.

In order to provide an unambiguous identification of the specific site of a polymorphism, sequences flanking the polymorphic site are shown in the tables, where the 5' and 3' flanking sequence is non-polymorphic, and the central position, shown in bold, is variable. It will be understood that there is no special significance to the length of non-polymorphic flanking sequence that is included, except to aid in positioning the polymorphism in the genomic sequence. The UGT2B exon sequences have been published, and therefore one of each pair of the sequences from exons in Tables 4, 7 and 10 are publically known sequence. The intron sequence has not been published, and hence both forms of this polymorphic sequence is novel.

As used herein, the term "UGT2B4, UGT2B7 and UGT2B15 genes" is intended to generically refer to both the wild-type and variant forms of the sequence, unless specifically denoted otherwise. As it is commonly used in the art, the term "gene" is intended to refer to the genomic region encompassing the 5' UTR, exons, introns, and the 3' UTR. Individual segments may be specifically referred to, *e.g.* exon 2, intron 5, *etc.* Combinations of such segments that provide for a complete UGT2B protein may be referred to generically as a protein coding sequence.

Nucleic acids of interest comprise the provided UGT2B^{v} nucleic acid sequence(s), as set forth in Tables 4, 7 and 10. Such nucleic acids include short hybridization probes, protein coding sequences, variant forms of UGT2B cDNA, segments, *e.g.* exons, introns, *etc.*, and the like. Methods of producing nucleic acids are well-known in the art, including chemical synthesis, cDNA or genomic cloning, PCR amplification, *etc.*

For the most part, DNA fragments will be of at least 15 nt, usually at least 20 nt, often at least 50 nt. Such small DNA fragments are useful as primers for PCR, hybridization screening, *etc.* Larger DNA fragments, *i.e.* greater than 100 nt are useful for production of the encoded polypeptide, promoter motifs, *etc.* For use in amplification reactions, such as PCR, a pair of primers will be used. The exact composition of primer sequences is not critical to the invention, but for most applications the primers will hybridize to the subject sequence under stringent conditions, as known in the art.

The UGT2B nucleic acid sequences are isolated and obtained in substantial purity, generally as other than an intact or naturally occurring mammalian chromosome. Usually, the DNA will be obtained substantially free of other nucleic acid sequences that do not include a UGT2B sequence or fragment thereof, generally being at least about 50%, usually at least about 90% pure and are typically "recombinant", i.e. flanked by one or more nucleotides with which it is not normally associated on a naturally occurring chromosome.

For screening purposes, hybridization probes of the polymorphic sequences may be used where both forms are present, either in separate reactions, spatially separated on a solid phase matrix, or labeled such that they can be distinguished from each other. Assays may utilize nucleic acids that hybridize to one or more of the described polymorphisms.

An array may include all or a subset of the polymorphisms listed in Tables 4, 7 and 10. One or both polymorphic forms may be present in the array, for example the polymorphism of SEQ ID NO:37 and 38 may be represented by either, or both, of the listed sequences. Usually such an array will include at least 2 different polymorphic sequences, *i.e.* polymorphisms located at unique positions within the locus, and may include all of the provided polymorphisms. Arrays of interest may further comprise sequences, including polymorphisms, of other genetic sequences, particularly other sequences of interest for pharmacogenetic screening, e.g. UGT1, other UGT2 sequences, cytochrome oxidase polymorphisms, *etc.* The oligonucleotide sequence on the array will usually be at least about 12 nt in length, may be the length of the provided polymorphic sequences, or may extend into the flanking regions to generate fragments of 100 to 200 nt in length. For examples of arrays, see Ramsay (1998) Nat. Biotech. 16:40-44; Hacia *et al.* (1996) Nature Genetics 14:441-447; Lockhart *et al.* (1996) Nature Biotechnol. 14:1675-1680; and De Risi *et al.* (1996) Nature Genetics 14:457-460.

Nucleic acids may be naturally occurring, *e.g.* DNA or RNA, or may be synthetic analogs, as known in the art. Such analogs may be preferred for use as probes because of superior stability under assay conditions. Modifications in the native structure, including alterations in the backbone, sugars or heterocyclic bases, have been shown to increase intracellular stability and binding affinity. Among useful changes in the backbone chemistry are phosphorothioates; phosphorodithioates, where both of the non-bridging oxygens are substituted with sulfur; phosphoroamidites; alkyl phosphotriesters and boranophosphates. Achiral phosphate derivatives include 3'-O'-5'-S-phosphorothioate, 3'-S-5'-O-phosphorothioate, 3'-CH2-5'-O-phosphonate and 3'-NH-5'-O-phosphoroamidate. Peptide nucleic acids replace the entire ribose phosphodiester backbone with a peptide linkage.

Sugar modifications are also used to enhance stability and affinity. The a-anomer of deoxyribose may be used, where the base is inverted with respect to the natural b-anomer. The 2'-OH of the ribose sugar may be altered to form 2'-O- methyl or 2'-O-allyl sugars, which provides resistance to degradation without compromising affinity.

Modification of the heterocyclic bases must maintain proper base pairing. Some useful substitutions include deoxyuridine for deoxythymidine; 5-methyl-2'- deoxycytidine and

5-bromo-2'-deoxycytidine for deoxycytidine. 5- propynyl-2'- deoxyuridine and 5-propynyl-2'-deoxycytidine have been shown to increase affinity and biological activity when substituted for deoxythymidine and deoxycytidine, respectively.

UGT2B polypeptides. A subset of the provided nucleic acid polymorphisms in UGT2B exons confer a change in the corresponding amino acid sequence. Using the amino acid sequence provided in SEQ ID NO:8 as a reference for UGT2B4, the amino acid polymorphisms of the invention include lys→asn, pos. 40; and glu→asp, pos. 454. Using the amino acid sequence provided in SEQ ID NO:40 as a reference for UGT2B7, the amino acid polymorphisms of the invention include leu→phe, pos. 107; thr→ile, pos. 179; and lys→gln, pos. 430. Using the amino acid sequence provided in SEQ ID NO:125 as a reference for UGT2B15, the amino acid polymorphisms of the invention include ser→gly, pos. 15; asp→tyr, pos. 85; leu→pro, pos. 170; his→gln, pos. 282; ala→val, pos. 398; val→ile, pos. 443; and thr→lys, pos. 523.

Polypeptides comprising at least one of the provided polymorphisms (UGT2B' polypeptides) are of interest. The term "UGT2B' polypeptides" as used herein includes complete UGT2B protein forms, *e.g.* such splicing variants as known in the art, and fragments thereof, which fragments may comprise short polypeptides, epitopes, functional domains; binding sites; *etc.*; and including fusions of the subject polypeptides to other proteins or parts thereof. Polypeptides will usually be at least about 8 amino acids in length, more usually at least about 12 amino acids in length, and may be 20 amino acids or longer, up to substantially the complete protein.

The UGT2B4, UGT2B7 and UGT2B15 genetic sequences, including polymorphisms, may be employed for polypeptide synthesis. For expression, an expression cassette may be employed, providing for a transcriptional and translational initiation region, which may be inducible or constitutive, where the coding region is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region. Various transcriptional initiation regions may be employed that are functional in the expression host. The polypeptides may be expressed in prokaryotes or eukaryotes in accordance with conventional ways, depending upon the purpose for expression. Small peptides can also prpared by chemical synthesis.

Substrate. A substrate is a chemical entity that is modified by UGT2B4, UGT2B7 or UGT2B15, usually under normal physiological conditions. Although the duration of drug action tends to be shortened by metabolic transformation, drug metabolism is not "detoxification". Frequently the metabolic product has greater biologic activity than the drug itself. In some cases the desirable pharmacologic actions are entirely attributable to metabolites, the administered drugs themselves being inert. Likewise, the toxic side effects of some drugs may be due in whole or in part to metabolic products.

Substrates can be either endogenous substrates, *i.e.* substrates normally found within the natural environment of UGT2B, such as estriol, or exogenous, *i.e.* substrates that are not normally found within the natural environment of UGT2B. UGT2B catalyzes glucuronidation of its substrates. The enzymes are specific for UDP-glucuronic acid, and not other UDP sugars.

Exemplary UGT2B4 substrates (*i.e.*, substrates of wild-type UGT2B4 and/or UGT2B4^{v} polypeptides) include, but are not necessarily limited to estriol and the catechol estrogens 4-hydroxyestrone, and 2-hydroxyestriol, 2-aminophenol, 4-methylumbellifereone, 1-naphthol, 4-hydroxybiphenyl and 4-nitrophenol, 2-aminophenol, 4-hydroxybiphenyl, menthol, *etc.*, among other substrates (Burchell *et al.* (1991) DNA Cell Biol **10**:487-494,Jin CJ, et al. (1993) Biochem Biophys Res Commun 194:496-503).

Exemplary UGT2B7 substrates (*i.e.*, substrates of wild-type UGT2B7 and/or UGT2B7^{v} polypeptides) include, but are not necessarily limited to oxazepam, hyodeoxycholic acid, estriol, S-naproxen, ketoprofen, ibuprofen, fenoprofen, clofibric acid (Patel *et al* (1995) Pharmacogenetics 5(1):43-49), morphine (Coffman *et al* (1997) Drug Metabolism and Disposition **25**:1-4), DMXAA (5,6-dimethylxantheonone-4-acetic acid) (Miners *et al* (1997) Cancer Res **57**:284), 2-Hydroxy AAF, 4 methylumbelliferone, carboxylic acid drugs (BP-7,8-trans diol) (Burchell *et al., supra.*)

Exemplary UGT2B15 substrates (*i.e.*, substrates of wild-type UGT2B15 and/or UGT2B15^{v} polypeptides) include, but are not necessarily limited to 4-hydroxybiphenyl, 1-naphthol, 4 methylumbelliferone , naringenin, eugenol (Burchell *et al., supra.*), simple phenolic compounds, 7-hydroxylated coumarins, flavonoids, anthraquinones; endogenous estrogens and androgens (Green *et al.* (1994) Drug Metabolism and Disposition **22**:799.

Modifier. A modifier is a chemical agent that modulates the action of a UGT2B molecule, either through altering its enzymatic activity (enzymatic modifier) or through

modulation of expression (expression modifier, *e.g.*, by affecting transcription or translation). In some cases the modifier may also be a substrate.

Pharmacokinetic parameters. Pharmacokinetic parameters provide fundamental data for designing safe and effective dosage regimens. A drug's volume of distribution, clearance, and the derived parameter, half-life, are particularly important, as they determine the degree of fluctuation between a maximum and minimum plasma concentration during a dosage interval, the magnitude of steady state concentration and the time to reach steady state plasma concentration upon chronic dosing. Parameters derived from *in vivo* drug administration are useful in determining the clinical effect of a particular UGT2B genotype.

Expression assay. An assay to determine the effect of a sequence polymorphism on UGT2B expression. Expression assays may be performed in cell-free extracts, or by transforming cells with a suitable vector. Alterations in expression may occur in the basal level that is expressed in one or more cell types, or in the effect that an expression modifier has on the ability of the gene to be inhibited or induced. Expression levels of a variant alleles are compared by various methods known in the art. Methods for determining promoter or enhancer strength include quantitation of the expressed natural protein; insertion of the variant control element into a vector with a reporter gene such as β-galactosidase, luciferase, chloramphenicol acetyltransferase, *etc.* that provides for convenient quantitation; and the like.

Gel shift or electrophoretic mobility shift assay provides a simple and rapid method for detecting DNA-binding proteins (Ausubel, F.M. *et al.* (1989) In: Current Protocols in Molecular Biology, Vol. 2, John Wiley and Sons, New York). This method has been used widely in the study of sequence-specific DNA-binding proteins, such as transcription factors. The assay is based on the observation that complexes of protein and DNA migrate through a nondenaturing polyacrylamide gel more slowly than free DNA fragments or double-stranded oligonucleotides. The gel shift assay is performed by incubating a purified protein, or a complex mixture of proteins (such as nuclear or cell extract preparations), with an end-labeled DNA fragment containing the putative protein binding site. The reaction products are then analyzed on a nondenaturing polyacrylamide gel. The specificity of the DNA-binding protein for the putative binding site is established by competition experiments using DNA fragments or oligonucleotides containing a binding site for the protein of interest, or other unrelated DNA sequences.

Expression assays can be used to detect differences in expression of polymorphisms with respect to tissue specificity, expression level, or expression in response to exposure to various substrates, and/or timing of expression during development. For example, since UGT2B4 is expressed in liver, polymorphisms could be evaluated for expression in tissues other than liver, or expression in liver tissue relative to a reference UGT2B4 polypeptide.

Substrate screening assay. Substrate screening assays are used to determine the metabolic activity of a UGT2B protein or peptide fragment on a substrate. Many suitable assays are known in the art, including the use of primary or cultured cells, genetically modified cells (*e.g.*, where DNA encoding the UGT2B polymorphism to be studied is introduced into the cell within an artificial construct), cell-free systems, *e.g.* microsomal preparations or recombinantly produced enzymes in a suitable buffer, or in animals, including human clinical trials (see, *e.g.*, Burchell et al. (1995) Life Sci. 57:1819-1831, specifically incorporated herein by reference. Where genetically modified cells are used, since most cell lines do not express UGT2B activity (liver cells lines being the exception), introduction of artificial construct for expression of the UGT2B polymorphism into many human and non-human cell lines does not require additional modification of the host to inactivate endogenous UGT2B expression/activity. Clinical trials may monitor serum, urine, *etc.* levels of the substrate or its metabolite(s).

Typically a candidate substrate is input into the assay system, and the conversion to a metabolite is measured over time. The choice of detection system is determined by the substrate and the specific assay parameters. Assays are conventionally run, and will include negative and positive controls, varying concentrations of substrate and enzyme, *etc.*

Genotyping: UGT2B genotyping is performed by DNA or RNA sequence and/or hybridization analysis of any convenient sample from a patient, *e.g.* biopsy material, blood sample (serum, plasma, etc.), buccal cell sample, etc. A nucleic acid sample from an individual is analyzed for the presence of polymorphisms in UGT2B, particularly those that affect the activity or expression of UGT2B. Specific sequences of interest include any polymorphism that leads to changes in basal expression in one or more tissues, to changes in the modulation of UGT2B expression by modifiers, or alterations in UGT2B substrate specificity and/or activity.

Linkage Analysis: Diagnostic screening may be performed for polymorphisms that are genetically linked to a phenotypic variant in UGT2B activity or expression, particularly through the use of microsatellite markers or SNPs. The microsatellite marker or SNP itself may not phenotypically expressed, but is linked to sequences that result in altered activity or expression. Two polymorphic variants may be in linkage disequilibrium, *i.e.* where alleles show non-random associations between genes even though individual loci are in Hardy-Weinberg equilibrium.

Linkage analysis may be performed alone, or in combination with direct detection of phenotypically evident polymorphisms. The use of microsatellite markers for genotyping is well documented. For examples, see Mansfield *et al.* (1994) Genomics 24:225-233; and Ziegle *et al.* (1992) Genomics 14:1026-1031. The use of SNPs for genotyping is illustrated in Underhill *et al.* (1996) Proc Natl Acad Sci U S A 93:196-200.

Transgenic animals. The subject nucleic acids can be used to generate genetically modified non-human animals or site specific gene modifications in cell lines. The term "transgenic" is intended to encompass genetically modified animals having a deletion or other knock-out of UGT2B4, UGT2B7 or UGT2B15 activity, having an exogenous UGT2B4, UGT2B7 or UGT2B15 gene that is stably transmitted in the host cells, or having an exogenous UGT2B promoter operably linked to a reporter gene. Transgenic animals may be made through homologous recombination, where the UGT2B locus is altered. Alternatively, a nucleic acid construct is randomly integrated into the genome. Vectors for stable integration include plasmids, retroviruses and other animal viruses, YACs, and the like. Of interest are transgenic mammals, *e.g.* cows, pigs, goats, horses, *etc.*, and particularly rodents, *e.g.* rats, mice, *etc.*

Genetically Modified Cells. Primary or cloned cells and cell lines are modified by the introduction of vectors comprising UGT2B4, UGT2B7 and UGT2B15 genetic polymorphisms. The gene may comprise one or more variant sequences, preferably a haplotype of commonly occurring combinations. In one embodiment of the invention, a panel of two or more genetically modified cell lines, each cell line comprising a UGT2B polymorphism, are provided for substrate and/or expression assays. The panel may further comprise cells genetically modified with other genetic sequences, including polymorphisms, particularly other sequences of interest for pharmacogenetic screening, e.g. UGT1, other UGT2 sequences, cytochrome oxidase polymorphisms, *etc.*

Vectors useful for introduction of the gene include plasmids and viral vectors, *e.g.* retroviral-based vectors, adenovirus vectors, *etc.* that are maintained transiently or stably in mammalian cells. A wide variety of vectors can be employed for transfection and/or integration of the gene into the genome of the cells. Alternatively, micro-injection may be employed, fusion, or the like for introduction of genes into a suitable host cell.

Genotyping Methods

The effect of a polymorphism in the UGT2B4, UGT2B7 or UGT2B15 gene sequence on the response to a particular substrate or modifier is determined by *in vitro* or *in vivo* assays. Such assays may include monitoring the metabolism of a substrate during clinical trials to determine the UGT2B enzymatic activity, specificity or expression level. Generally, *in vitro* assays are useful in determining the direct effect of a particular polymorphism, while clinical studies will also detect an enzyme phenotype that is genetically linked to a polymorphism.

The response of an individual to the substrate or modifier can then be predicted by determining the UGT2B genotype, with respect to the polymorphism. Where there is a differential distribution of a polymorphism by racial background, guidelines for drug administration can be generally tailored to a particular ethnic group.

The basal expression level in different tissue may be determined by analysis of tissue samples from individuals typed for the presence or absence of a specific polymorphism. Any convenient method may be used, *e.g.* ELISA, RIA, *etc.* for protein quantitation, northern blot or other hybridization analysis, quantitative RT-PCR, *etc.* for mRNA quantitation. The tissue specific expression is correlated with the genotype.

The alteration of UGT2B expression in response to a modifier is determined by administering or combining the candidate modifier with an expression system, *e.g.* animal, cell, *in vitro* transcription assay, etc. The effect of the modifier on UGT2B transcription and/or steady state mRNA levels is determined. As with the basal expression levels, tissue specific interactions are of interest. Correlations are made between the ability of an expression modifier to affect UGT2B activity, and the presence of the provided polymorphisms. A panel of different modifiers, cell types, etc. may be screened in order to determine the effect under a number of different conditions.

A UGT2B polymorphism that results in altered enzyme activity or specificity is determined by a variety of assays known in the art. The enzyme may be tested for metabolism of a substrate *in vitro*, for example in defined buffer, or in cell or subcellular

lysates, where the ability of a substrate to be metabolized by UGT2B4, UGT2B7 or UGT2B15 under physiologic conditions is determined. Where there are not significant issues of toxicity from the substrate or metabolite(s), *in vivo* human trials may be utilized, as previously described.

The genotype of an individual is determined with respect to the provided UGT2B4, UGT2B7 and UGT2B15 polymorphisms. The genotype is useful for determining the presence of a phenotypically evident polymorphism, and for determining the linkage of a polymorphism to phenotypic change.

A number of methods are available for analyzing nucleic acids for the presence of a specific sequence. Where large amounts of DNA are available, genomic DNA is used directly. Alternatively, the region of interest is cloned into a suitable vector and grown in sufficient quantity for analysis. The nucleic acid may be amplified by conventional techniques, such as the polymerase chain reaction (PCR), to provide sufficient amounts for analysis. The use of the polymerase chain reaction is described in Saiki *et al.* (1985) Science **230**:1350-1354, and a review of current techniques may be found in Sambrook *et al.* Molecular Cloning: A Laboratory Manual, CSH Press 1989, pp.14.2-14.33. Amplification may be used to determine whether a polymorphism is present, by using a primer that is specific for the polymorphism. Alternatively, various methods are known in the art that utilize oligonucleotide ligation as a means of detecting polymorphisms, for examples see Riley *et al.* (1990) Nucleic Acids Res **18**:2887-2890; and Delahunty *et al.* (1996) Am J Hum Genet **58**:1239-1246.

A detectable label may be included in an amplification reaction. Suitable labels include fluorochromes, e.g. fluorescein isothiocyanate (FITC), rhodamine, Texas Red, phycoerythrin, allophycocyanin, 6-carboxyfluorescein (6-FAM), 2',7'-dimethoxy-4',5'-dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2',4',7',4,7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA), radioactive labels, e.g. ^{32}P, ^{35}S, ^{3}H; etc. The label may be a two stage system, where the amplified DNA is conjugated to biotin, haptens, etc. having a high affinity binding partner, e.g. avidin, specific antibodies, etc., where the binding partner is conjugated to a detectable label. The label may be conjugated to one or both of the primers. Alternatively, the pool of nucleotides used in the amplification is labeled, so as to incorporate the label into the amplification product.

The sample nucleic acid, *e.g.* amplified or cloned fragment, is analyzed by one of a number of methods known in the art. The nucleic acid may be sequenced by dideoxy or

other methods. Hybridization with the variant sequence may also be used to determine its presence, by Southern blots, dot blots, *etc.* The hybridization pattern of a control and variant sequence to an array of oligonucleotide probes immobilized on a solid support, as described in U.S. 5,445,934, or in WO95/35505, may also be used as a means of detecting the presence of variant sequences. Single strand conformational polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), mismatch cleavage detection, and heteroduplex analysis in gel matrices are used to detect conformational changes created by DNA sequence variation as alterations in electrophoretic mobility. Alternatively, where a polymorphism creates or destroys a recognition site for a restriction endonuclease (restriction fragment length polymorphism, RFLP), the sample is digested with that endonuclease, and the products size fractionated to determine whether the fragment was digested. Fractionation is performed by gel or capillary electrophoresis, particularly acrylamide or agarose gels.

In one embodiment of the invention, an array of oligonucleotides are provided, where discrete positions on the array are complementary to one or more of the provided polymorphic sequences, e.g. oligonucleotides of at least 12 nt, frequently 20 nt, or larger, and including the sequence flanking the polymorphic position. Such an array may comprise a series of oligonucleotides, each of which can specifically hybridize to a different polymorphism. For examples of arrays, see Hacia *et al.* (1996) Nat Genet **14**:441-447 and DeRisi *et al.* (1996) Nat Genet **14**:457-460.

The genotype information is used to predict the response of the individual to a particular UGT2B substrate or modifier. Where an expression modifier inhibits UGT2B expression, then drugs that are a UGT2B substrate will be metabolized more slowly if the modifier is co-administered. Where an expression modifier induces UGT2B expression, a co-administered substrate will typically be metabolized more rapidly. Similarly, changes in UGT2B activity will affect the metabolism of an administered drug. The pharmacokinetic effect of the interaction will depend on the metabolite that is produced, *e.g.* a prodrug is metabolized to an active form, a drug is metabolized to an inactive form, an environmental compound is metabolized to a toxin, *etc.* Consideration is given to the route of administration, drug-drug interactions, drug dosage, *etc.*

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention,

and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (*e.g.*, amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

EXAMPLE 1

Genotyping UGT2B4

Materials and Methods

DNA Samples. Blood specimens from approximately 48 individuals were collected after obtaining informed consent. All samples were stripped of personal identifiers to maintain confidentiality. The only data associated with a given blood samples was gender and self-reported major racial group designations in the United States (Caucasian, Hispanic, African American). Genomic DNA was isolated from these samples using standard techniques. DNA was stored either as a concentrated solution, or in a dried form in microtiter plates.

PCR amplifications. The primers used to amplify exons in which polymorphisms were found are shown in Table 1, and were designed with NBI's Oligo version 5.1 program. Sequences for exons in which no polymorphisms were found are not shown.

Table 1. UGT2B4 PCR Primers.

	Primary PCR Amplification		
Region	Forward/ Reverse	SEQ ID NO	Sequence
UGT2B4Exon 1	F	9.	Tacctttagttgtctctttgtca
	R	10.	Ttcctggagtcttctgtatga
UGT2B4Exon 4	F	11.	Catcccttgttcttctcatt
	R	12.	Cgggactggaaaataaatat
UGT2B4Exon 6	F	13.	Ggggtttcaccgtgtta
	R	14.	Aaagccaagcagcactaa

Twenty-five nanograms of gDNA were amplified in the primary amplifications using the Perkin Elmer GeneAmp PCR kit according to the manufacturer's instructions in 25 µl reactions with AmpliTaq Gold DNA polymerase. Reactions contained 25 mM $MgCl_2$ and 0.2 µM of each primer. Thermal cycling was performed using a GeneAmp PCR System 9600

PCR machine (Perkin Elmer), utilizing a touch-down PCR protocol. The protocol, unless indicated otherwise in Table 2, consisted of an initial incubation of 95°C for 10 min, followed by ten cycles of 95°C for 20 sec, 64°C (minus 1°C per cycle) for 20 sec, 72°C for 2 min, six cycles of 95°C for 20 sec, 54°C for 20 sec, 72°C for 2 min, and nineteen cycles of 95°C for 20 sec, 54°C for 20 sec, 72°C for 2 min (plus 15 sec per cycle), and one final extension step of 72°C for 10 min.

For the secondary PCR reactions, one microliter of each primary PCR reaction was re-amplified using the primary PCR primers. The thermal cycling profile that was used for the primary PCR for an exon was also used for the secondary PCR.

Table 2.
Cycling Profile Modifications

Exon	Primary PCR	Secondary PCR
1	Touch-Down PCR step: 8 cycles	same as Primary PCR
	64° C (minus 1° C per cycle), for 15 sec	
	Total Number of cycles: 35	
4	Touch-Down PCR step: 10 cycles	same as Primary PCR
	64° C (minus 1° C per cycle), for 15 sec	
	Total Number of cycles: 35	
6	Touch-Down PCR step: 7 cycles	same as Primary PCR
	64° C (minus 1° C per cycle), for 15 sec	
	Total Number of cycles: 35	

DNA sequencing. PCR products from 48 individuals (approximately 1/3 African American, 1/3 Caucasian, 1/3 Hispanic) were prepared for sequencing by treating 8 µl of each PCR product with 0.15 µl of exonuclease I (1.5 U/reaction), 0.3 µl of Shrimp Alkaline Phosphatase (0.3U/reaction), q.s. to 10 µl with MilliQ water, and incubated at 37°C for 30 min, followed by 72°C for 15 min. Cycle sequencing was performed on the GeneAmp PCR System 9600 PCR machine (Perkin Elmer) using the ABI Prism dRhodamine Terminator Cycle Sequencing Ready Reaction Kit according to the manufacturer's directions, with the following changes: (1) 2 µl of dRhodamine terminator premix, instead of 8 µl, (2) 10% (v/v) Dimethylsulfoxide was added to each individual nucleotide. The oligonucleotide primers (unlabelled), at 3 picomoles per reaction, used for the sequencing reactions are listed in

Table 3. Sequencing reactions, with a final volume of 5 µl, were subjected to 25 cycles at 96°C for 10 sec, 50°C for 5 sec, and 60°C for 4 min, followed by ethanol precipitation. After decanting the ethanol, samples were evaporated to dryness using a SpeedVac for roughly 15 min and were resuspended in 2 µl of loading buffer (5:1 deionized formamide:50 mM EDTA pH 8.0), heated to 94°C for 2 min, and were electrophoresed through 5.25% polyacrylamide/6M urea gels in an ABI Prism 377 DNA Sequencer, according to the manufacturer's instructions for sequence determination. All sequences were determined from both the 5' and 3' (sense and antisense) direction.

Table 3. Sequencing Primers

P. No.	F/R	SEQ ID NO	Forward Primer
1	F	15.	Ccacatgctcagactgttaa
	R	16.	Caaaaataccccactaccc
2	F	17.	Cccttgttcttctcattgtta
	R	18.	Ttcagtaagcttgtttcatgat
3,4	F	19.	Cctggccaaattgactt
	R	20.	Caggaacccagtcacatc
5	F	21.	Ggggaaaagagattaattacg
	R	22.	Agccaagcagcactaatc
6,7	F	23.	Tccaattcacaggttacatg
	R	24.	Agccaagcagcactaatc

Table 4.
Summary of UGT2B4 polymorphisms.

Exon	Nt change	AA change	SEQ ID	Sequence
1	G 157 C	Lys 40 Asn	25.	Tggatgaatataaagacaatcctggat
			26.	Tggatgaatataaacacaatcctggat
Int.4	T 61 C		27.	Aagtgttaatagttatcatgaaacaag
			28.	Aagtgttaatagctatcatgaaacaag
6	T 1411 A	Glu 454 Asp	29.	Tgaagcccttgatcgagcagtcttct
			30.	Tgaagcccttgaacgagcagtcttct
6	C 1412 A		31.	Tgaagcccttgatcgagcagtcttct
			32.	Tgaagcccttgatagagcagtcttct
6	T 1849 C		33.	Gatataaagccatacgaggttatattg
			34.	Gatataaagccatatgaggttatattg
6	A 1919 C		35.	Caggttacatgaaaaaaaatttacta
			36.	Caggttacatgaaaaacaatttacta
6	A 2072 G		37.	Ttgttgaggaagctaataaataattaa
			38.	Ttgttgaggaaactaataaataattaa

Nucleotide variants in exons are numbered from first base in Sequence 1. Amino Acid changes are numbered beginning with the first methionine in the protein sequence provided in Sequence 1. The nucleotide variant in intron 4 is numbered from the beginning of intron 4, as provided in Sequence 2.4.

EXAMPLE 2
UGT2B7 Genotyping

Twenty-five nanograms of gDNA were amplified in the primary amplifications using the Perkin Elmer GeneAmp PCR kit according to the manufacturer's instructions in 25 µl reactions with AmpliTaq Gold DNA polymerase. Reactions contained 25 mM $MgCl_2$ and 0.2 µM of each primer. Thermal cycling was performed using a GeneAmp PCR System 9600 PCR machine (Perkin Elmer), utilizing a touch-down PCR protocol. The exons for UGT2B7 were amplified using the following cycling conditions: An initial incubation at 96°C for 10 min., followed by 16 cycles of 95°C for 20 sec., 52°C for 20 sec., 72°C for 2 min., and nineteen cycles of 95°C for 20 sec, 52°C for 20 sec, 72°C for 2 min (plus 15 sec per cycle), and one final extension step of 72°C for 10 min.

For the secondary PCR reactions, one microliter of each primary PCR reaction was re-amplified using the primary PCR primers. The thermal cycling profile that was used for the primary PCR for an exon was also used for the secondary PCR.

The amplification primers are provided in Table 5, the sequencing primers in Table 6, and the polymorphisms in Table 7.

Table 5
PCR Primers for UGT2B7 Amplification

Region		SEQ ID NO	Primer Sequence
UGT2B7 Exon 1	Primary F	46.	Cttggctaatttatctttgg
	Primary R	47.	Cccactaccctgactttat
	Secondary F	48.	Ggacataaccatgagaaatg
	Secondary R	49.	Agctctgcttcaaagacac
UGT2B7 Exon 2	Primary F	50.	Tgtccgtatgctactattgaa
	Primary R	51.	Tgtgctaatccctttgtaaat
	Secondary F	52.	Ttttttttctattcctgtcag
	Secondary R	53.	Ctttaccccacccattt
UGT2B7 Exon 4	Primary F	54.	Cccttgatctcattcctact
	Primary R	55.	Aactggctattctttagatgtatg
	Secondary F	56.	Cattcctactctttatacagttctc
	Secondary R	57.	Cccccgattcagactat
UGT2B7 Exon 5	Primary F	58.	Cccttgatctcattcctact
	Primary R	59.	Aactggctattctttagatgtatg
	Secondary F	60.	Tcctccgaagtctgaaac
	Secondary R	61.	Tataaaaaggatgaaactcacac
UGT2B7 Exon 6	Primary F	62.	Caagcccccaagttatgt
	Primary R	63.	Cagtaggatccgcgatataa
	Secondary F	64.	Tctgaggggttttgtctgta
	Secondary R	65.	Ccgcgatataagttcaacaa

DNA sequencing. PCR products from 48 individuals were prepared for sequencing by treating 8 µL of each PCR product with 0.15 µL of exonuclease I (1.5U/reaction), 0.3 µL of Shrimp Alkaline Phosphatase (0.3U/reaction), q.s. to 10 µL with MilliQ water, and incubated at 37°C for 30 min, followed by 72°C for 15 min. Cycle sequencing was performed

on the GeneAmp PCR System 9600 PCR machine (Perkin Elmer) using the ABI Prism dRhodamine Terminator Cycle Sequencing Ready Reaction Kit or the ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction Kit according to the manufacturer's directions, with the following changes: For the ABI Prism dRhodamine Terminator kit, (1) 2 µL of dRhodamine terminator premix, instead of 8 µL, (2) 10% (v/v) Dimethylsulfoxide was added to each individual nucleotide, (3) 5 µL total volume instead of 20 µL. For the ABI Prism Big Dye Terminator kit (1) 0.8 µL of Big Dye terminator premix, instead of 8 µL, and (2) 15 µL total volume instead of 20 µL. The oligonucleotide primers (unlabeled), at 3 picomoles per reaction, used for the sequencing reactions are listed in Table 6. Sequencing reactions, with a final volume of 5 µL, were subjected to 25 cycles at 96°C for 10 sec, 50°C for 5 sec, and 60°C for 4 min, followed by ethanol precipitation. After decanting the ethanol, samples were evaporated to dryness using a SpeedVac for roughly 15 min and were resuspended in 2 µl of loading buffer (5:1 delonized formamide:50 mM EDTA pH 8.0), heated to 94°C for 2 min, and were electrophoresed through 5.25% polyacrylamide/6M urea gels in an ABI Prism 377 DNA Sequencer, according to the manufacturer's instructions for sequence determination. All sequences were determined from both the 5' and 3' (sense and antisense) direction.

Table 6
Sequencing Primers UGT2B7

P. No.	F/R	SEQ ID NO	Primer Sequence
1, 2	F	66.	Ggacataaccatgagaaatg
	R	67.	Ttaagagcggatgagttgt
3,4	F	68.	Tcatcatgcaacagattaag
	R	69.	Cactacagggaaaaatagca
5	F	70.	Acccttgtgtacagtctca
	R	71.	Agctctgcttcaaagacac
6, 7	F	72.	Ttgcctacattattctaaccc
	R	73.	Ctttaccccacccattt
8, 9	F	74.	Cattcctactctttatacagttctc
	R	75.	Cccccgattcagactat
10	F	76.	Cattcctactctttatacagttctc
	R	77.	Cccccgattcagactat
11, 12	F	78.	Tcctccgaagtctgaaac
	R	79.	Tataaaaaggatgaaactcacac
13	F	80.	Tctgaggggttttgtctgta
	R	81.	Tttttgtctcaggaagaaaga
14	F	82.	Aaaaaaagaaaaaaaaatcttttc
	R	83.	Ccgcgatataagttcaacaa

Table 7
Summary of Sequence Polymorphisms UGT2B7

N	Exon	Nt change	AA change	SEQ ID NO.	Sequence
1	1	G 13 A		84.	Tgcattgcaccaggatgtctgt
				85.	Tgcattgcaccaagatgtctgt
2	1	T 151 C	Leu 107 Phe	86.	Tcctggatgagcttattcagaga
				87.	Tcctggatgagcctattcagaga
3	1	A 236 T		88.	Cattttggttatattttcac
				89.	Cattttggttttattttcac
4	1	A 286 G		90.	Cataactagaaagttctgtaa
				91.	Cataactaggaagttctgtaa
5	1	C 450 T	Thr 179 Ile	92.	Cctggctacacttttgaaaa
				93.	Cctggctacattttgaaaa
6	2	A 14 G		94.	Gaagacccactacattatctg
				95.	Gaagacccactacgttatctg
7	2	AT 80-81 TC		96.	Aattttcagtttccatatccactctt
				97.	Aattttcagtttcctcatccactctt
8	4	C 57 G		98.	Taggtctcaatactcggctcta
				99.	Taggtctcaatactcggctgta
9	4	C 60 T		100.	Tacaagtggataccccaga
				101.	Tataagtggataccccaga
10	In.4	A 154 del		102.	Gggagaaagaatacattataattttt
				103.	Gggagaaagaatacttataattttt
11	5	C 101 T		104.	Ttccattgtttgccgatcaac
				105.	Ttccattgtttgctgatcaac
12	5	A 198 C	Lys 430 Gln	106.	Gaatgcattgaagagagtaat
				107.	Gaatgcattgcagagagtaat
13	6	A 197 G		108.	Ctggtctgtgtggcaactgtga
				109.	Ctggtctgtgtggcgactgtga
14	6	C 528 A		110.	Taagataaagccttatgag
				111.	Taagataaagacttatgag

Example 3

Genotyping UGT2B15

Sequencing and analysis were performed as described in Example 2. The amplification primers are provided in Table 9, the sequencing primers in Table 8, and the polymorphisms in Table 10.

Table 8
Sequencing Primers UGT2B15

Region		SEQ ID NO	Primer Sequence
UGT2B15 Exon 1	Primary F	119.	catgcacctattcagactgt
	Primary R	120.	tgggtgtcctgtagtagtga
	Secondary F	121.	attgatttttcctcagatataagta
	Secondary R	122.	tcataatttcccttaaaaacac
UGT2B15 Exon 2	Primary F	123.	atatgtttgggtatgttattcc
	Primary R	124.	ccatattcccctcactct
	Secondary F	125.	atacctgcatattcaaataacaa
	Secondary R	126.	tatccagccattccttct
UGT2B15 Exon 5	Primary F	127.	agttttgtgggtataatgttac
	Primary R	128.	aaacgggttaaaattcata
	Secondary F	129.	tcataccttgtaattaataattttg
	Secondary R	130.	cgggttaaaattcatattca
UGT2B15 Exon 6	Primary F	131.	tcatgccaattcagtgac
	Primary R	132.	accctccatgctgaaat
	Secondary F	133.	tcaaagaccatccatagactt
	Secondary R	134.	ggagtcccatctttcagtc

Table 9
PCR Primers UGT2B15

P. No.	F/R	SEQ ID NO	Primer Sequence
1,2	F	135.	Attgatttttcctcagatataagta
	R	136.	Atttactggcattgacaag
3	F	137.	Attgatttttcctcagatataagta
	R	138.	Tgtacagaaagggtatgttaaa
4	F	139.	aaaaat g/t atttggaagattc
	R	140.	Tcataatttcccttaaaaacac
5	F	141.	Atacctgcatattcaaataacaa
	R	142.	Tatccagccattccttct
6,7	F	143.	Tcataccttgtaattaataattttg
	R	144.	Cgggttaaaattcatattca
8,9	F	145.	Tcaaagaccatccatagactt
	R	146.	Ggagtcccatctttcagtc

Table 10
Summary of Sequence Polymorphisms UGT2B15

N	Exon	Ntd change	AA change	SEQ ID NO.	Sequence
1	1	A 53 G	Ser 15 Gly	147.	tgatacagctcagttgttac
				148.	tgatacagctcggttgttac
2	1	T 184 G		149.	tgttgacatcttcggcttct
				150.	tgttgacatcgtcggcttct
3	1	G 263 T	Asp 85 Tyr	151.	ctttaactaaaaatgatttggaa
				152.	ctttaactaaaaattatttggaa
4	1	T 519 C	Leu 170 Pro	153.	tttaacatacccttctgtaca
				154.	tttaacatacccttccgtaca
5	2	C 122 G	His 282 Gln	155.	ttggaggacttcactgtaaacc
				156.	ttggaggacttcagtgtaaacc
6	5	G 59 A		157.	tatgaggcgatctaccatgggat
				158.	tatgaggcaatctaccatgggat
7	5	C 100 T	Ala 398 Val	159.	cccttgtttgcggatcaacatgat
				160.	cccttgtttgtggatcaacatgat
8	6	G 14 A	Val 443 Ile	161.	aaagagaatgtcatgaaattat
				162.	aaagagaatatcatgaaattat
9	6	C 523 A	Thr 523 Lys	163.	gcttgccaaaacaggaaagaa
				164.	gcttgccaaaaaaggaaagaa

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Claims

What is Claimed is:

1. An isolated nucleic acid molecule comprising a UGT2B sequence polymorphism of SEQ ID NOs:25-38; 84-111 or 147-164, as part of other than a naturally occurring chromosome.

2. A nucleic acid probe for detection of UGT2B locus polymorphisms, comprising a polymorphic sequence of SEQ ID NOs:25-38; 84-111 or 147-164.

3. A nucleic acid probe according to Claim 2, wherein said probe is conjugated to a detectable marker.

4. An array of oligonucleotides comprising:

two or more probes for detection of UGT2B locus polymorphisms, said probes comprising at least one form of a polymorphic sequences of SEQ ID NOs:25-38; 84-111 or 147-164.

5. A method for detecting in an individual a polymorphism in a UGT2B metabolism of a substrate, the method comprising:

analyzing the genome of said individual for the presence of at least one UGT2B polymorphism of SEQ ID NOs:25-38; 84-111 or 147-164; wherein the presence of said predisposing polymorphism is indicative of an alteration in UGT2B expression or activity.

6. A method according to Claim 5, wherein said analyzing step comprises detection of specific binding between the genomic DNA of said individual with an array of oligonucleotides comprising:

two or more probes for detection of UGT2B locus polymorphisms, said probes comprising at least one form of a polymorphic sequence of SEQ ID NOs:25-38; 84-111 or 147-164.

7. A method according to Claim 5, wherein said alteration in UGT2B expression is tissue specific.

8. A method according to Claim 5, wherein said alteration in UGT2B expression is in response to a UGT2B modifier.

9. A method according to Claim 8, wherein said modifier induces UGT2B expression.

10. A method according to Claim 8, wherein said modifier inhibits UGT2B expression.

SEQUENCE LISTING

<110> Penny, Laura
Galvin, Margaret
Miller, Andrew
Reidy, Michael

<120> Genotyping Human
UDP-Glucuronosyltransferase 2B4 (UGT2B4), 2B7 (UGT2B7) and
2B15 (UGT2B15) Genes

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Ser Ala Leu Leu Leu Ile Gln Leu Ser Cys Tyr Phe Ser Ser Gly Ser
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Cys Gly Lys Val Leu Val Trp Pro Thr Glu Phe Ser His Trp Met Asn
        25                  30                  35

ata aag aca atc ctg gat gaa ctt gtc cag aga ggt cat gag gtg act      199
Ile Lys Thr Ile Leu Asp Glu Leu Val Gln Arg Gly His Glu Val Thr
    40                  45                  50

gta ttg gca tct tca gct tcc att tct ttc gat ccc aac agc cca tct      247
Val Leu Ala Ser Ser Ala Ser Ile Ser Phe Asp Pro Asn Ser Pro Ser
55                  60                  65                  70

act ctt aaa ttt gaa gtt tat cct gta tct tta act aaa act gag ttt      295
Thr Leu Lys Phe Glu Val Tyr Pro Val Ser Leu Thr Lys Thr Glu Phe
                75                  80                  85

gag gat att atc aag cag ctg gtt aag aga tgg gca gaa ctt cca aaa      343
Glu Asp Ile Ile Lys Gln Leu Val Lys Arg Trp Ala Glu Leu Pro Lys
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Lys Leu Met Lys Lys Leu Gln Glu Ser Arg Phe Asp Val Val Leu Ala
135                 140                 145                 150

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            170                 175                 180

cat agt gga gga ctt ctg ttc cct cct tcc tat gtg cct gtt gtt atg      631
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        185                 190                 195

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Ser Glu Leu Ser Asp Gln Met Thr Phe Ile Glu Arg Val Lys Asn Met
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Ser Glu Thr Met Ala Lys Ala Asp Ile Trp Leu Ile Arg Asn Tyr Trp
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        265                 270                 275

gga ctc cac tgc aaa cct gcc aaa ccc cta ccg aag gaa atg gaa gag      919
Gly Leu His Cys Lys Pro Ala Lys Pro Leu Pro Lys Glu Met Glu Glu
    280                 285                 290

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Phe Val Gln Ser Ser Gly Glu Asn Gly Val Val Val Phe Ser Leu Gly
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tcg atg gtc agt aac acg tca gaa gaa agg gcc aat gta att gca tca     1015
Ser Met Val Ser Asn Thr Ser Glu Glu Arg Ala Asn Val Ile Ala Ser
                315                 320                 325

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            330                 335                 340

aaa cca gat act tta gga ctc aat act cgg ctg tac aag tgg ata ccc     1111
Lys Pro Asp Thr Leu Gly Leu Asn Thr Arg Leu Tyr Lys Trp Ile Pro
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cag aat gat ctt ctt ggt cac cca aaa acc aga gct ttt ata act cat     1159
Gln Asn Asp Leu Leu Gly His Pro Lys Thr Arg Ala Phe Ile Thr His
    360                 365                 370

ggt gga gcc aat ggc atc tat gag gca atc tac cat gga atc cct atg     1207
Gly Gly Ala Asn Gly Ile Tyr Glu Ala Ile Tyr His Gly Ile Pro Met
375                 380                 385                 390

gtg ggc gtt cca ttg ttt gca gat caa cct gat aac att gca cac atg     1255
Val Gly Val Pro Leu Phe Ala Asp Gln Pro Asp Asn Ile Ala His Met
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Thr Asp Leu Leu Asn Ala Leu Lys Thr Val Ile Asn Asp Pro Leu Tyr
        425                 430                 435

aaa gag aat gct atg aaa tta tca aga att cat cat gat caa cca gtg     1399
Lys Glu Asn Ala Met Lys Leu Ser Arg Ile His His Asp Gln Pro Val
    440                 445                 450

aag ccc ctt gat cga gca gtc ttc tgg att gaa ttt gtc atg cgc cat     1447
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455                 460                 465                 470

aaa gga gcc aag cac ctt cgg gtt gca gcc cac gac ctc acc tgg ttc     1495
Lys Gly Ala Lys His Leu Arg Val Ala Ala His Asp Leu Thr Trp Phe
                475                 480                 485

cag tac cac tct ttg gat gtg act ggg ttc ctg ctg gcc tgt gtg gca     1543
Gln Tyr His Ser Leu Asp Val Thr Gly Phe Leu Leu Ala Cys Val Ala
            490                 495                 500

act gtg ata ttc atc atc aca aaa tgt ctg ttt tgt gtc tgg aag ttt     1591
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Arg Gly His Glu Val Thr Val Leu Ala Ser Ser Ala Ser Ile Ser Phe
    50                  55                  60
Asp Pro Asn Ser Pro Ser Thr Leu Lys Phe Glu Val Tyr Pro Val Ser
65                  70                  75                  80
Leu Thr Lys Thr Glu Phe Glu Asp Ile Ile Lys Gln Leu Val Lys Arg
                85                  90                  95
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Gln Glu Ile Met Trp Thr Phe Asn Asp Ile Leu Arg Lys Phe Cys Lys
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145                 150                 155                 160
Ala Glu Leu Leu Lys Ile Pro Phe Val Tyr Ser Leu Arg Phe Ser Pro
                165                 170                 175
Gly Tyr Ala Ile Glu Lys His Ser Gly Gly Leu Leu Phe Pro Pro Ser
            180                 185                 190
Tyr Val Pro Val Val Met Ser Glu Leu Ser Asp Gln Met Thr Phe Ile
        195                 200                 205
Glu Arg Val Lys Asn Met Ile Tyr Val Leu Tyr Phe Glu Phe Trp Phe
    210                 215                 220
Gln Ile Phe Asp Met Lys Lys Trp Asp Gln Phe Tyr Ser Glu Val Leu
225                 230                 235                 240
Gly Arg Pro Thr Thr Leu Ser Glu Thr Met Ala Lys Ala Asp Ile Trp
                245                 250                 255
Leu Ile Arg Asn Tyr Trp Asp Phe Gln Phe Pro His Pro Leu Leu Pro
            260                 265                 270
Asn Val Glu Phe Val Gly Gly Leu His Cys Lys Pro Ala Lys Pro Leu
        275                 280                 285
Pro Lys Glu Met Glu Glu Phe Val Gln Ser Ser Gly Glu Asn Gly Val
    290                 295                 300
Val Val Phe Ser Leu Gly Ser Met Val Ser Asn Thr Ser Glu Glu Arg
305                 310                 315                 320
Ala Asn Val Ile Ala Ser Ala Leu Ala Lys Ile Pro Gln Lys Val Leu
                325                 330                 335
Trp Arg Phe Asp Gly Asn Lys Pro Asp Thr Leu Gly Leu Asn Thr Arg
            340                 345                 350
Leu Tyr Lys Trp Ile Pro Gln Asn Asp Leu Leu Gly His Pro Lys Thr
        355                 360                 365
Arg Ala Phe Ile Thr His Gly Gly Ala Asn Gly Ile Tyr Glu Ala Ile
    370                 375                 380
Tyr His Gly Ile Pro Met Val Gly Val Pro Leu Phe Ala Asp Gln Pro
385                 390                 395                 400
Asp Asn Ile Ala His Met Lys Ala Lys Gly Ala Ala Val Ser Leu Asp
                405                 410                 415
Phe His Thr Met Ser Ser Thr Asp Leu Leu Asn Ala Leu Lys Thr Val
            420                 425                 430
Ile Asn Asp Pro Leu Tyr Lys Glu Asn Ala Met Lys Leu Ser Arg Ile
        435                 440                 445
His His Asp Gln Pro Val Lys Pro Leu Asp Arg Ala Val Phe Trp Ile
    450                 455                 460
Glu Phe Val Met Arg His Lys Gly Ala Lys His Leu Arg Val Ala Ala
465                 470                 475                 480
His Asp Leu Thr Trp Phe Gln Tyr His Ser Leu Asp Val Thr Gly Phe
                485                 490                 495
Leu Leu Ala Cys Val Ala Thr Val Ile Phe Ile Ile Thr Lys Cys Leu
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Phe Cys Val Trp Lys Phe Val Arg Thr Gly Lys Lys Gly Lys Arg Asp
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1 5 10

caa ctg agc ttt tgc ttt agc tct ggg aat tgt gga aag gtg ctg gtg 98
Gln Leu Ser Phe Cys Phe Ser Ser Gly Asn Cys Gly Lys Val Leu Val
15 20 25

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tgg gca gca gaa tac agc cat tgg atg aat ata aag aca atc ctg gat      146
Trp Ala Ala Glu Tyr Ser His Trp Met Asn Ile Lys Thr Ile Leu Asp
     30                  35                  40

gag ctt att cag aga ggt cat gag gtg act gta ctg gca tct tca gct      194
Glu Leu Ile Gln Arg Gly His Glu Val Thr Val Leu Ala Ser Ser Ala
 45                  50                  55                  60

tcc att ctt ttt gat ccc aac aac tca tcc gct ctt aaa att gaa att      242
Ser Ile Leu Phe Asp Pro Asn Asn Ser Ser Ala Leu Lys Ile Glu Ile
                 65                  70                  75

tat ccc aca tct tta act aaa act gag ttg gag aat ttc atc atg caa      290
Tyr Pro Thr Ser Leu Thr Lys Thr Glu Leu Glu Asn Phe Ile Met Gln
            80                  85                  90

cag att aag aga tgg tca gac ctt cca aaa gat aca ttt tgg tta tat      338
Gln Ile Lys Arg Trp Ser Asp Leu Pro Lys Asp Thr Phe Trp Leu Tyr
        95                 100                 105

ttt tca caa gta cag gaa atc atg tca ata ttt ggt gac ata act aga      386
Phe Ser Gln Val Gln Glu Ile Met Ser Ile Phe Gly Asp Ile Thr Arg
    110                 115                 120

aag ttc tgt aaa gat gta gtt tca aat aag aaa ttt atg aaa aaa gta      434
Lys Phe Cys Lys Asp Val Val Ser Asn Lys Lys Phe Met Lys Lys Val
125                 130                 135                 140

caa gag tca aga ttt gac gtc att ttt gca gat gct att ttt ccc tgt      482
Gln Glu Ser Arg Phe Asp Val Ile Phe Ala Asp Ala Ile Phe Pro Cys
                145                 150                 155

agt gag ctg ctg gct gag cta ttt aac ata ccc ttt gtg tac agt ctc      530
Ser Glu Leu Leu Ala Glu Leu Phe Asn Ile Pro Phe Val Tyr Ser Leu
            160                 165                 170

agc ttc tct cct ggc tac act ttt gaa aag cat agt gga gga ttt att      578
Ser Phe Ser Pro Gly Tyr Thr Phe Glu Lys His Ser Gly Gly Phe Ile
        175                 180                 185

ttc cct cct tcc tac gta cct gtt gtt atg tca gaa tta act gat caa      626
Phe Pro Pro Ser Tyr Val Pro Val Val Met Ser Glu Leu Thr Asp Gln
    190                 195                 200

atg act ttc atg gag agg gta aaa aat atg atc tat gtg ctt tac ttt      674
Met Thr Phe Met Glu Arg Val Lys Asn Met Ile Tyr Val Leu Tyr Phe
205                 210                 215                 220

gac ttt tgg ttc gaa ata ttt gac atg aag aag tgg gat cag ttt tat      722
Asp Phe Trp Phe Glu Ile Phe Asp Met Lys Lys Trp Asp Gln Phe Tyr
                225                 230                 235

agt gaa gtt cta gga aga ccc act aca tta tct gag aca atg ggg aaa      770
Ser Glu Val Leu Gly Arg Pro Thr Thr Leu Ser Glu Thr Met Gly Lys
            240                 245                 250

gct gac gta tgg ctt att cga aac tcc tgg aat ttt cag ttt cca tat      818
Ala Asp Val Trp Leu Ile Arg Asn Ser Trp Asn Phe Gln Phe Pro Tyr
        255                 260                 265

cca ctc tta cca aat gtt gat ttt gtt gga gga ctc cac tgc aaa cct      866
Pro Leu Leu Pro Asn Val Asp Phe Val Gly Gly Leu His Cys Lys Pro
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    270                 275                 280

gcc aaa ccc ctg cct aag gaa atg gaa gac ttt gta cag agc tct gga      914
Ala Lys Pro Leu Pro Lys Glu Met Glu Asp Phe Val Gln Ser Ser Gly
285                 290                 295                 300

gaa aat ggt gtt gtg gtg ttt tct ctg ggg tca atg gtc agt aac atg      962
Glu Asn Gly Val Val Val Phe Ser Leu Gly Ser Met Val Ser Asn Met
                305                 310                 315

aca gaa gaa agg gcc aac gta att gca tca gcc ctg gcc cag atc cca     1010
Thr Glu Glu Arg Ala Asn Val Ile Ala Ser Ala Leu Ala Gln Ile Pro
            320                 325                 330

caa aag gtt ctg tgg aga ttt gat ggg aat aaa cca gat acc tta ggt     1058
Gln Lys Val Leu Trp Arg Phe Asp Gly Asn Lys Pro Asp Thr Leu Gly
        335                 340                 345

ctc aat act cgg ctc tac aag tgg ata ccc cag aat gac ctt cta ggt     1106
Leu Asn Thr Arg Leu Tyr Lys Trp Ile Pro Gln Asn Asp Leu Leu Gly
    350                 355                 360

cat cca aag acc aga gct ttt ata act cat ggt gga gcc aat ggc atc     1154
His Pro Lys Thr Arg Ala Phe Ile Thr His Gly Gly Ala Asn Gly Ile
365                 370                 375                 380

tac gag gca atc tac cat ggg atc cct atg gtg ggg att cca ttg ttt     1202
Tyr Glu Ala Ile Tyr His Gly Ile Pro Met Val Gly Ile Pro Leu Phe
                385                 390                 395

gcc gat caa cct gat aac att gct cac atg aag gcc agg gga gca gct     1250
Ala Asp Gln Pro Asp Asn Ile Ala His Met Lys Ala Arg Gly Ala Ala
            400                 405                 410

gtt aga gtg gac ttc aac aca atg tcg agt aca gac ttg ctg aat gca     1298
Val Arg Val Asp Phe Asn Thr Met Ser Ser Thr Asp Leu Leu Asn Ala
        415                 420                 425

ttg aag aga gta att aat gat cct tca tat aaa gag aat gtt atg aaa     1346
Leu Lys Arg Val Ile Asn Asp Pro Ser Tyr Lys Glu Asn Val Met Lys
    430                 435                 440

tta tca aga att caa cat gat caa cca gtg aag ccc ctg gat cga gca     1394
Leu Ser Arg Ile Gln His Asp Gln Pro Val Lys Pro Leu Asp Arg Ala
445                 450                 455                 460

gtc ttc tgg att gaa ttt gtc atg cgc cac aaa gga gct aaa cac ctt     1442
Val Phe Trp Ile Glu Phe Val Met Arg His Lys Gly Ala Lys His Leu
                465                 470                 475

cgg gtt gca gcc cac gac ctc acc tgg ttc cag tac cac tct ttg gat     1490
Arg Val Ala Ala His Asp Leu Thr Trp Phe Gln Tyr His Ser Leu Asp
            480                 485                 490

gtg att ggg ttc ctg ctg gtc tgt gtg gca act gtg ata ttt atc gtc     1538
Val Ile Gly Phe Leu Leu Val Cys Val Ala Thr Val Ile Phe Ile Val
        495                 500                 505

aca aaa tgt tgt ctg ttt tgt ttc tgg aag ttt gct aga aaa gca a       1584
Thr Lys Cys Cys Leu Phe Cys Phe Trp Lys Phe Ala Arg Lys Ala
    510                 515                 520
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agaagggaaa aaatgattag ttatatctga gatttgaagc tggaaaacct gataggtgag   1644
actacttcag tttattccag caagaaagat tgtgatgcaa gatttctttc ttcctgagac   1704
aaaaaaaaaa aaagaaaaaa aaatcttttc aaaatttact ttgtcaaata aaaatttgtt   1764
tttcagagat ttaccaccca gttcatggtt agaaatattt tgtggcaatg aagaaaacac   1824
tacggaaaat aaaaaataag ataaagcctt                                   1854
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<400> 40

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            20                  25                  30
Tyr Ser His Trp Met Asn Ile Lys Thr Ile Leu Asp Glu Leu Ile Gln
        35                  40                  45
Arg Gly His Glu Val Thr Val Leu Ala Ser Ser Ala Ser Ile Leu Phe
    50                  55                  60
Asp Pro Asn Asn Ser Ser Ala Leu Lys Ile Glu Ile Tyr Pro Thr Ser
65                  70                  75                  80
Leu Thr Lys Thr Glu Leu Glu Asn Phe Ile Met Gln Gln Ile Lys Arg
                85                  90                  95
Trp Ser Asp Leu Pro Lys Asp Thr Phe Trp Leu Tyr Phe Ser Gln Val
            100                 105                 110
Gln Glu Ile Met Ser Ile Phe Gly Asp Ile Thr Arg Lys Phe Cys Lys
        115                 120                 125
Asp Val Val Ser Asn Lys Lys Phe Met Lys Lys Val Gln Glu Ser Arg
    130                 135                 140
Phe Asp Val Ile Phe Ala Asp Ala Ile Phe Pro Cys Ser Glu Leu Leu
145                 150                 155                 160
Ala Glu Leu Phe Asn Ile Pro Phe Val Tyr Ser Leu Ser Phe Ser Pro
                165                 170                 175
Gly Tyr Thr Phe Glu Lys His Ser Gly Gly Phe Ile Phe Pro Pro Ser
            180                 185                 190
Tyr Val Pro Val Val Met Ser Glu Leu Thr Asp Gln Met Thr Phe Met
        195                 200                 205
Glu Arg Val Lys Asn Met Ile Tyr Val Leu Tyr Phe Asp Phe Trp Phe
    210                 215                 220
Glu Ile Phe Asp Met Lys Lys Trp Asp Gln Phe Tyr Ser Glu Val Leu
225                 230                 235                 240
Gly Arg Pro Thr Thr Leu Ser Glu Thr Met Gly Lys Ala Asp Val Trp
                245                 250                 255
Leu Ile Arg Asn Ser Trp Asn Phe Gln Phe Pro Tyr Pro Leu Leu Pro
            260                 265                 270
Asn Val Asp Phe Val Gly Gly Leu His Cys Lys Pro Ala Lys Pro Leu
        275                 280                 285
Pro Lys Glu Met Glu Asp Phe Val Gln Ser Ser Gly Glu Asn Gly Val
    290                 295                 300
Val Val Phe Ser Leu Gly Ser Met Val Ser Asn Met Thr Glu Glu Arg
305                 310                 315                 320
Ala Asn Val Ile Ala Ser Ala Leu Ala Gln Ile Pro Gln Lys Val Leu
                325                 330                 335
Trp Arg Phe Asp Gly Asn Lys Pro Asp Thr Leu Gly Leu Asn Thr Arg
            340                 345                 350
Leu Tyr Lys Trp Ile Pro Gln Asn Asp Leu Leu Gly His Pro Lys Thr
        355                 360                 365
Arg Ala Phe Ile Thr His Gly Gly Ala Asn Gly Ile Tyr Glu Ala Ile
    370                 375                 380
Tyr His Gly Ile Pro Met Val Gly Ile Pro Leu Phe Ala Asp Gln Pro
385                 390                 395                 400
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Asp Asn Ile Ala His Met Lys Ala Arg Gly Ala Ala Val Arg Val Asp
                405                 410                 415
Phe Asn Thr Met Ser Ser Thr Asp Leu Leu Asn Ala Leu Lys Arg Val
            420                 425                 430
Ile Asn Asp Pro Ser Tyr Lys Glu Asn Val Met Lys Leu Ser Arg Ile
        435                 440                 445
Gln His Asp Gln Pro Val Lys Pro Leu Asp Arg Ala Val Phe Trp Ile
    450                 455                 460
Glu Phe Val Met Arg His Lys Gly Ala Lys His Leu Arg Val Ala Ala
465                 470                 475                 480
His Asp Leu Thr Trp Phe Gln Tyr His Ser Leu Asp Val Ile Gly Phe
                485                 490                 495
Leu Leu Val Cys Val Ala Thr Val Ile Phe Ile Val Thr Lys Cys Cys
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Leu Phe Cys Phe Trp Lys Phe Ala Arg Lys Ala Lys
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<400> 41

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attgcataag acagatggca tgtccataca agatccttga tattagctga aggatagcac     180
tcataaacat aaaagggaaa ttaatcacat ctgtgtgaac agatcattta ccttcatttg     240
tctctttgcc atccacatgc tcagactgtt gatttaatga tattgtatgt actttgactt     300
ataagggtta cattttaact tcttggctaa tttatctttg gacataacca tgagaaatga     360
cagaaaggaa cagcaactgg aaaacaagca ttgcattgca ccaggatgtc tgtgaaatgg     420
acttcagtaa ttttgctaat acaactgagc ttttgcttta gctctgggaa ttgtggaaag     480
gtgctggtgt gggcagcaga atacagccat tggatgaata taaagacaat cctggatgag     540
cttattcaga gaggtcatga ggtgactgta ctggcatctt cagcttccat tctttttgat     600
cccaacaact catccgctct taaaattgaa atttatccca catctttaac taaaactgag     660
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aatattatta agatcttagc ttgaatctaa aagagtagtt ggtacaagga tttcagccat 180
actctcaaca tagtccacag ttcacttgaa ccaaagataa aagaattagc ttaatgagtt 240
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atggagctca aagagttgtt taaatgtccg tatgctacta ttgaagcttt aagagaaaag 360
aaatttttatg tttaactttc tatggctcat tttaataatt gtttatgatt atgagcatac 420
tgatgcgaca ttagagatgt agcttaacct cacaattctc ctactacttt gtctttctta 480
taaatacaca tgggcaaaat atgtaataca taaaattaaa ttatatctat atatgaatat 540
gtgtatatat ttttcaaagc acagatattt gcctacattt ttgcctacat tattctaacc 600
cctttcagaa atttacctaa agtaattatc ttgtgtcatc caccttttt ttttctattc 660
ctgtcaggaa gacccactac attatctgag acaatgggga aagctgacgt atggcttatt 720
cgaaactcct ggaattttca gtttccatat ccactcttac caaatgttga ttttgttgga 780
ggactccact gcaaacctgc caaacccctg cctaaggtaa acatactttt gttggtttta 840
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ctacttcaaa agatagaata tgtgcaagta ataaaaatta tataaaaact attatctgaa 1260
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<212> DNA
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ttttttagtt tttgaaaaac taccagaaaa ctctgaacaa actttaagtg aagtataaag 180
cattgtagag aaacataaat gtagatataa aattatccca actgtgagta gcttatcctc 240
agagctcata gttagggaag taaaccacta actgtttcca actaagagaa ttctacagaa 300
aacctgcctg aaataaacac aagggattta gtagaacaac aatataggat taaagctgag 360
tggtcccact ttccaagaac ctatattagt aactttagta atgaaagtga agagtcgtgt 420
attaatattt ttaacattat ctccctgaca acaatgtaat agctccattt cttttctccc 480
ttacacacat gcacacaaat acatacacat acacacatat ttacacaaat atccttaaca 540
gcatccacct atctcatatt atacatctac ttgcaaaaaa actgagtgat tgggtcagtt 600
aaaaaatatt atttactcca ataattcctc aaaatactgg attttctctc tttagtaatt 660
tgcaccaatt cttttggtag tgcccgctgt gctaatactc ttttgtgatg aagcaaattc 720
tttcttcaca ggaaatggaa gactttgtac agagctctgg agaaaatggt gttgtggtgt 780
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aaggagctaa acaccttcgg gttgcagccc acgacctcac ctggttccag taccactctt 180
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gttgtctgtt ttgtttctgg aagtttgcta gaaaagcaaa gaagggaaaa aatgattagt 300
tatatctgag atttgaagct ggaaaacctg ataggtgaga ctacttcagt ttattccagc 360
aagaaagatt gtgatgcaag atttctttct tcctgagaca aaaaaaaaaa aagaaaaaaa 420
aatcttttca aaatttactt tgtcaaataa aaatttgttt ttcagagatt taccacccag 480
ttcatggtta gaaatatttt gtggcaatga agaaaacact acggaaaata aaaaataaga 540
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ctc agt tgt tac ttt agc tct gga agc tgt gga aag gtg cta gtg tgg 97
Leu Ser Cys Tyr Phe Ser Ser Gly Ser Cys Gly Lys Val Leu Val Trp
15 20 25

ccc aca gaa tac agc cat tgg ata aat atg aag aca atc ctg gaa gag 145
Pro Thr Glu Tyr Ser His Trp Ile Asn Met Lys Thr Ile Leu Glu Glu
30 35 40 45

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ctt gtt cag agg ggt cat gag gtg act gtg ttg aca tct tcg gct tct      193
Leu Val Gln Arg Gly His Glu Val Thr Val Leu Thr Ser Ser Ala Ser
                 50                  55                  60

act ctt gtc aat gcc agt aaa tca tct gct att aaa tta gaa gtt tat      241
Thr Leu Val Asn Ala Ser Lys Ser Ser Ala Ile Lys Leu Glu Val Tyr
            65                  70                  75

cct aca tct tta act aaa aat gat ttg gaa gat tct ctt ctg aaa att      289
Pro Thr Ser Leu Thr Lys Asn Asp Leu Glu Asp Ser Leu Leu Lys Ile
        80                  85                  90

ctc gat aga tgg ata tat ggt gtt tca aaa aat aca ttt tgg tca tat      337
Leu Asp Arg Trp Ile Tyr Gly Val Ser Lys Asn Thr Phe Trp Ser Tyr
    95                  100                 105

ttt tca caa tta caa gaa ttg tgt tgg gaa tat tat gac tac agt aac      385
Phe Ser Gln Leu Gln Glu Leu Cys Trp Glu Tyr Tyr Asp Tyr Ser Asn
110                 115                 120                 125

aag ctc tgt aaa gat gca gtt ttg aat aag aaa ctt atg atg aaa cta      433
Lys Leu Cys Lys Asp Ala Val Leu Asn Lys Lys Leu Met Met Lys Leu
                130                 135                 140

caa gag tca aag ttt gat gtc att ctg gca gat gcc ctt aat ccc tgt      481
Gln Glu Ser Lys Phe Asp Val Ile Leu Ala Asp Ala Leu Asn Pro Cys
            145                 150                 155

ggt gag cta ctg gct gaa cta ttt aac ata ccc ttt ctg tac agt ctt      529
Gly Glu Leu Leu Ala Glu Leu Phe Asn Ile Pro Phe Leu Tyr Ser Leu
        160                 165                 170

cga ttc tct gtt ggc tac aca ttt gag aag aat ggt gga gga ttt ctg      577
Arg Phe Ser Val Gly Tyr Thr Phe Glu Lys Asn Gly Gly Gly Phe Leu
    175                 180                 185

ttc cct cct tcc tat gta cct gtt gtt atg tca gaa tta agt gat caa      625
Phe Pro Pro Ser Tyr Val Pro Val Val Met Ser Glu Leu Ser Asp Gln
190                 195                 200                 205

atg att ttc atg gag agg ata aaa aat atg ata cat atg ctt tat ttt      673
Met Ile Phe Met Glu Arg Ile Lys Asn Met Ile His Met Leu Tyr Phe
                210                 215                 220

gac ttt tgg ttt caa att tat gat ctg aag aag tgg gac cag ttt tat      721
Asp Phe Trp Phe Gln Ile Tyr Asp Leu Lys Lys Trp Asp Gln Phe Tyr
            225                 230                 235

agt gaa gtt cta gga aga ccc act aca tta ttt gag aca atg ggg aaa      769
Ser Glu Val Leu Gly Arg Pro Thr Thr Leu Phe Glu Thr Met Gly Lys
        240                 245                 250

gct gaa atg tgg ctc att cga acc tat tgg gat ttt gaa ttt cct cgc      817
Ala Glu Met Trp Leu Ile Arg Thr Tyr Trp Asp Phe Glu Phe Pro Arg
    255                 260                 265

cca ttc tta cca aat gtt gat ttt gtt gga gga ctt cac tgt aaa cca      865
Pro Phe Leu Pro Asn Val Asp Phe Val Gly Gly Leu His Cys Lys Pro
270                 275                 280                 285

gcc aaa ccc ctg cct aag gaa atg gaa gag ttt gtg cag agc tct gga      913
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Ala Lys Pro Leu Pro Lys Glu Met Glu Glu Phe Val Gln Ser Ser Gly
                290                 295                 300

gaa aat ggt att gtg gtg ttt tct ctg ggg tcg atg atc agt aac atg      961
Glu Asn Gly Ile Val Val Phe Ser Leu Gly Ser Met Ile Ser Asn Met
            305                 310                 315

tca gaa gaa agt gcc aac atg att gca tca gcc ctt gcc cag atc cca     1009
Ser Glu Glu Ser Ala Asn Met Ile Ala Ser Ala Leu Ala Gln Ile Pro
        320                 325                 330

caa aag gtt cta tgg aga ttt gat ggc aag aag cca aat act tta ggt     1057
Gln Lys Val Leu Trp Arg Phe Asp Gly Lys Lys Pro Asn Thr Leu Gly
    335                 340                 345

tcc aat act cga ctg tac aag tgg tta ccc cag aat gac ctt ctt ggt     1105
Ser Asn Thr Arg Leu Tyr Lys Trp Leu Pro Gln Asn Asp Leu Leu Gly
350                 355                 360                 365

cat ccc aaa acc aaa gct ttt ata act cat ggt gga acc aat ggc atc     1153
His Pro Lys Thr Lys Ala Phe Ile Thr His Gly Gly Thr Asn Gly Ile
                370                 375                 380

tat gag gcg atc tac cat ggg atc cct atg gtg ggc att ccc ttg ttt     1201
Tyr Glu Ala Ile Tyr His Gly Ile Pro Met Val Gly Ile Pro Leu Phe
            385                 390                 395

gcg gat caa cat gat aac att gct cac atg aaa gcc aag gga gca gcc     1249
Ala Asp Gln His Asp Asn Ile Ala His Met Lys Ala Lys Gly Ala Ala
        400                 405                 410

ctc agt gtg gac atc agg acc atg tca agt aga gat ttg ctc aat gca     1297
Leu Ser Val Asp Ile Arg Thr Met Ser Ser Arg Asp Leu Leu Asn Ala
    415                 420                 425

ttg aag tca gtc att aat gac cct gtc tat aaa gag aat gtc atg aaa     1345
Leu Lys Ser Val Ile Asn Asp Pro Val Tyr Lys Glu Asn Val Met Lys
430                 435                 440                 445

tta tca aga att cat cat gac caa cca atg aag ccc ctg gat cga gca     1393
Leu Ser Arg Ile His His Asp Gln Pro Met Lys Pro Leu Asp Arg Ala
                450                 455                 460

gtc ttc tgg att gag ttt gtc atg cgc cac aaa gga gcc aag cac ctt     1441
Val Phe Trp Ile Glu Phe Val Met Arg His Lys Gly Ala Lys His Leu
            465                 470                 475

cga gtc gca gct cac aac ctc acc tgg atc cag tac cac tct ttg gat     1489
Arg Val Ala Ala His Asn Leu Thr Trp Ile Gln Tyr His Ser Leu Asp
        480                 485                 490

gtg ata gca ttc ctg ctg gcc tgc gtg gca act gtg ata ttt atc atc     1537
Val Ile Ala Phe Leu Leu Ala Cys Val Ala Thr Val Ile Phe Ile Ile
    495                 500                 505

aca aaa ttt tgc ctg ttt tgt ttc cga aag ctt gcc aaa aca gga aag     1585
Thr Lys Phe Cys Leu Phe Cys Phe Arg Lys Leu Ala Lys Thr Gly Lys
510                 515                 520                 525

aag aag aaa aga g attagttata tcaaaagcct gaagtggaat gactgaaaga      1638
Lys Lys Lys Arg
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tgggactcct cctttatttc agcatggagg gttttaaatg gaggatttcc tttttcctgt   1698
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tacgtacttt agttggaatt attctatgtc aatgattttt aagctatgaa aaatacaatg   1818
gggggaagga tagcatttgg agatatacct aatgttaaat gacgagttac tggatgcagc   1878
acgccaacat ggcacatgta tacatatgta gctaacctca cgttgtgcac atgtacccta   1938
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            20                  25                  30
Tyr Ser His Trp Ile Asn Met Lys Thr Ile Leu Glu Glu Leu Val Gln
        35                  40                  45
Arg Gly His Glu Val Thr Val Leu Thr Ser Ser Ala Ser Thr Leu Val
    50                  55                  60
Asn Ala Ser Lys Ser Ser Ala Ile Lys Leu Glu Val Tyr Pro Thr Ser
65                  70                  75                  80
Leu Thr Lys Asn Asp Leu Glu Asp Ser Leu Leu Lys Ile Leu Asp Arg
                85                  90                  95
Trp Ile Tyr Gly Val Ser Lys Asn Thr Phe Trp Ser Tyr Phe Ser Gln
            100                 105                 110
Leu Gln Glu Leu Cys Trp Glu Tyr Tyr Asp Tyr Ser Asn Lys Leu Cys
        115                 120                 125
Lys Asp Ala Val Leu Asn Lys Lys Leu Met Met Lys Leu Gln Glu Ser
    130                 135                 140
Lys Phe Asp Val Ile Leu Ala Asp Ala Leu Asn Pro Cys Gly Glu Leu
145                 150                 155                 160
Leu Ala Glu Leu Phe Asn Ile Pro Phe Leu Tyr Ser Leu Arg Phe Ser
                165                 170                 175
Val Gly Tyr Thr Phe Glu Lys Asn Gly Gly Gly Phe Leu Phe Pro Pro
            180                 185                 190
Ser Tyr Val Pro Val Val Met Ser Glu Leu Ser Asp Gln Met Ile Phe
        195                 200                 205
Met Glu Arg Ile Lys Asn Met Ile His Met Leu Tyr Phe Asp Phe Trp
    210                 215                 220
Phe Gln Ile Tyr Asp Leu Lys Lys Trp Asp Gln Phe Tyr Ser Glu Val
225                 230                 235                 240
Leu Gly Arg Pro Thr Thr Leu Phe Glu Thr Met Gly Lys Ala Glu Met
                245                 250                 255
Trp Leu Ile Arg Thr Tyr Trp Asp Phe Glu Phe Pro Arg Pro Phe Leu
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INTERNATIONAL SEARCH REPORT

rnational Application No
PCT/US 99/16675

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEVESQUE E. ET AL.,: "Isolation and characterization of UGT2B15 : a UDP-Glucuronosyltransferase encoded by a polymorphic gene" PHARMACOGENETICS, vol. 7, no. 4, - August 1997 (1997-08) pages 317-325, XP000852552 cited in the application see whole doc. esp. results p.320 ff. -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 1999	22/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Müller, F

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INTERNATIONAL SEARCH REPORT

National Application No
PCT/US 99/16675

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RITTER J.K. ET AL.,: "Cloning and expression of human liver UDP-glucuronosyltransferase in COS-1 cells" J. BIOL. CHEMISTRY, vol. 265, no. 14, - 15 May 1990 (1990-05-15) pages 7900-7906, XP002121919 the whole document	1-3
X	JIN. C_J. ET AL.,: "cDNA cloning and expression of two new members of the human liver UDP-glucuronosyltransferase 2B subfamily" BIOCHEM. BIOPHYS. RESEARCH COMMUNICATIONS, vol. 194, no. 1, - 15 July 1993 (1993-07-15) pages 496-503, XP002121839 cited in the application the whole document	1-3
X	WO 92 12987 A (US) 6 August 1992 (1992-08-06) see whole doc. esp. claims and summary	1-10
A	RITTER J.K. ET AL.,: "Cloning of two human liver bilirubin UDP-glucuronosyl-transferase cDNAs with expression in COS-1 cells" J. BIOL. CHEMISTRY, vol. 266, no. 2, - 15 January 1991 (1991-01-15) pages 1043-1047, XP002121838 the whole document	1-3
A	GREEN M D ET AL: "STABLE EXPRESSION OF A HUMAN LIVER UDP-GLUCURONOSYLTRANSFERASE (UGT2B15) WITH ACTIVITY TOWARD STEROID AND XENOBIOTIC SUBSTRATES" DRUG METABOLISM AND DISPOSITION, vol. 22, no. 5, 1 September 1994 (1994-09-01), pages 799-805, XP002039718 ISSN: 0090-9556 cited in the application	
A	CIOTTI ET AL: "GENETIC POLYMORPHISM IN THE HUMAN UGT1A6 (PLANAR PHENOL) UDP -GLUCURONOSYLTRANSFERASE: PHARMACOLOGICAL IMPLICATIONS" PHARMACOGENETICS, vol. 7, no. 7, 1997, pages 485-495 495, XP002113205 ISSN: 0960-314X the whole document	

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INTERNATIONAL SEARCH REPORT

National Application No
PCT/US 99/16675

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	DE WILDT S.N. ET AL.,: "Glucuronidation in humans" CLIN. PHARMACOKINETICS, vol. 36, no. 6, - June 1999 (1999-06) pages 439-452, XP002121840 the whole document	
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